THE EFFECT OF PLASMA-CHOLESTEROL-LOWERING DIET IN MALE SURVIVORS OF MYOCARDIAL INFARCTION

A Controlled Clinical Trial*

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The purpose of this study was to ascertain what effect a reduction of the plasma cholesterol concentration by means of diet would have on morbidity and mortality from coronary heart disease (CHD relapses) in male survivors of myocardial infarction.

Material and Methods

The present trial studied 412 males aged 30 to 64 discharged from medical departments in Oslo during the years 1956 to 1958 with a first diagnosis of myocardial infarction. The men were allocated at random to the experimental diet group and to the control group, one to two years after their infarction. At the start of the trial it was decided that each patient should stay in the trial for exactly five years.

The comparability of the groups was thoroughly studied, and it was found that they were strictly comparable except for blood pressure. However, blood pressure was slightly higher in the diet group.

A close follow-up was undertaken to include clinical examination with diet and weight control, serum-cholesterol determination, electrocardiography, and a review of hospital records.

The cholesterol-lowering diet was low in animal fats and in dietary cholesterol, and rich in vegetable oil.

In an analysis of the experimental diet as consumed by 17 selected dieters, the mean daily intake was: protein, 92 gm.; fat, 104 gm.; carbo-

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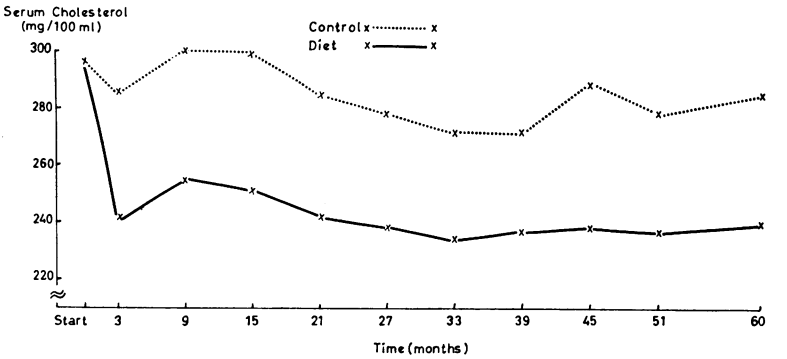

Fig. 1. Serum cholesterol levels in the diet and the control group during the period of observation.

	N (at start)	*Start value (mg./100 ml.)*	*Mean reduction (mg.)*	*Mean reduction (per cent)*
Control	206	296	11	3.7
Diet	206	296	52	17.6

hydrates, 269 gm.; and cholesterol, 264 mg. Daily intake of calories was 2,387. Calories derived from fat constituted 39 per cent of the total. The sources of fat were: soy bean oil (72 per cent), fish fat (11.6 per cent), animal fat (8.8 per cent), cereal fat (5.0 per cent), and fat from other sources (2.6 per cent). Of the mean dietary fat, 21.6 per cent was saturated, 25.7 monounsaturated, and 52.7 polyunsaturated. The mean reduction of serum cholesterol in these 17 dieters was 31 per cent.

Emphasis was laid on enduring and energetic dietary training. Adherence to the diet was controlled by close personal contact, the physician being assisted by a full time, experienced dietician who worked in the homes of the patients. The degree of adherence was quantified by means of a detailed questionnaire used six times during the period of observation. According to a constructed list of scores, 62.2 per cent of the dieters were judged to be excellent adherents, 22.1 per cent good, 10.3 per cent fair, and 5.4 per cent poor or reluctant.

Judging by personal contact with the controls and by a questionnaire used at the end of the trial, and also by the serum-cholesterol level, which remained nearly unchanged from the beginning to the end, it can be assumed that the type of food in the control group remained largely unchanged.

At the start of the trial the mean serum-cholesterol value was exactly the same in the two groups (296 mg. per 100 ml.). From the

TABLE I.—TOTAL INCIDENCE OF CHD RELAPSES

A. Total number of CHD relapses

	Diet group	*Control group*
Myocardial reinfarctions	43	64
Acquired angina pectoris	10 (also reinfarction 2)	29 (also reinfarction 9)
Sudden death	27 (also reinfarction 4) (also acq. angina 1)	27 (also reinfarction 7) (also acq. angina 4)
Total	80	120

B. Total number of patients with CHD relapses

	Diet group	*Control group*	*P-value*
Myocardial reinfarction	34 (fatal 10)	54 (fatal 23)	0.022 (0.029)
Acquired angina pectoris	8	20	0.031
Sudden death	22	16	>0.05
Total	64	90	.011

first control examination, three months later, and throughout, a significant difference in the serum cholesterol level persisted (Figure 1). The mean cholesterol reduction in the diet group was 17.6 per cent against 3.7 per cent in the control group. Of the dieters, 123 obtained a serum cholesterol reduction greater than or equal to 15 per cent, against 27 of the controls.

RESULTS

In the final calculations only one CHD relapse was counted in each patient; the order of priority was as follows: myocardial reinfarction, new cases of angina pectoris, and sudden death. Criteria for the diagnosis of reinfarction were established, the decision being left to a diagnostic board which did not know to which group the patient belonged.

In the diet group 43 myocardial reinfarctions occurred in 34 patients; 10 of the reinfarctions were fatal. In the control group 64 myocardial reinfarctions occurred in 54 patients; 23 of the reinfarctions were fatal (Table I). The difference between the groups is statistically significant (reinfarction patients: $x^2 = 5.22$, $p = 0.022$, fatal reinfarction: $x^2 = 4.74$, $p = 0.029$). The difference did not become statistically significant until the third year of the trial.

Of 75 dieters and 79 controls who did not have angina pectoris at the start of the trial, 10 dieters and 29 controls acquired angina during

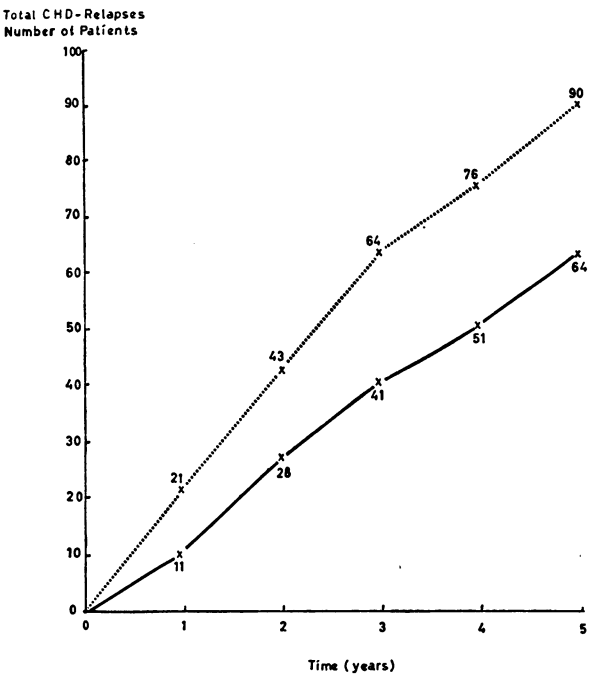

Fig. 2. Cumulated incidence of total CHD relapses.

the period of observation. Of these, two of the dieters and nine of the controls also had reinfarctions, and have been counted as such. After excluding these patients the difference between the groups is still statistically significant ($x^2 = 4.61$, $p = 0.031$). The number of cases of sudden death was the same in the two groups, 27 in each.

The total number of CHD relapses was 80 in the diet group and 120 in the control group. These relapses occurred in 64 dieters and in 90 controls. The difference is statistically significant ($x^2 = 6.48$, $p = 0.011$), and the difference became significant during the second year of the trial (Figure 2).

CHD Relapses in Relation to Various Factors

When patients were divided into age groups, those below 60 years and those 60 years and above, it was found that the difference in the CHD relapse rate was statistically significant only in patients below the age of 60. So, too, was the relapse combination, myocardial infarction and acquired angina pectoris. The incidence of sudden death was the

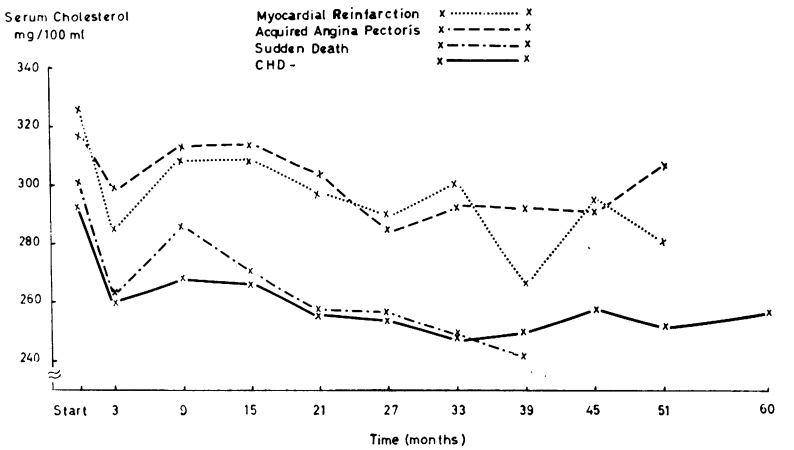

Fig. 3. Both groups together. Age < 60. Mean serum cholesterol levels during the period of observation in patients with different types of CHD relapses, and in the relapse-free.

same in the two groups, independently of age.

In the diet group as well as in the control group, the serum cholesterol level was higher in the patients with CHD relapses than in those without. Subdivision of the material revealed that this difference in the serum cholesterol level was also limited to those under 60 years of age who had myocardial reinfarctions and acquired angina pectoris (Figure 3). At the age of 60 and above there was no difference in the serum cholesterol level between those with and without CHD relapses.

No association was found between the serum cholesterol level and the incidence of sudden death in either of the two age groups.

Body weight had no definite influence on the serum cholesterol level or on the CHD relapse rate, except that the cholesterol level tended to be reduced in those who were underweight.

Blood pressure had no definite influence on the CHD relapse rate in the diet group. In the control group there was a strong trend, though statistically not significant, toward a higher CHD relapse rate in the hypertensives. This was especially true when serum cholesterol at the start was equal to or greater than 275 mg. per 100 ml. The difference in the CHD relapses between these normotensive and hypertensive controls escapes the five per cent level of significance very narrowly ($x^2 = 3.22$, $p = 0.073$).

Smoking habits did not influence the serum cholesterol level or the CHD relapse rate in the control group. In the smoking dieters there

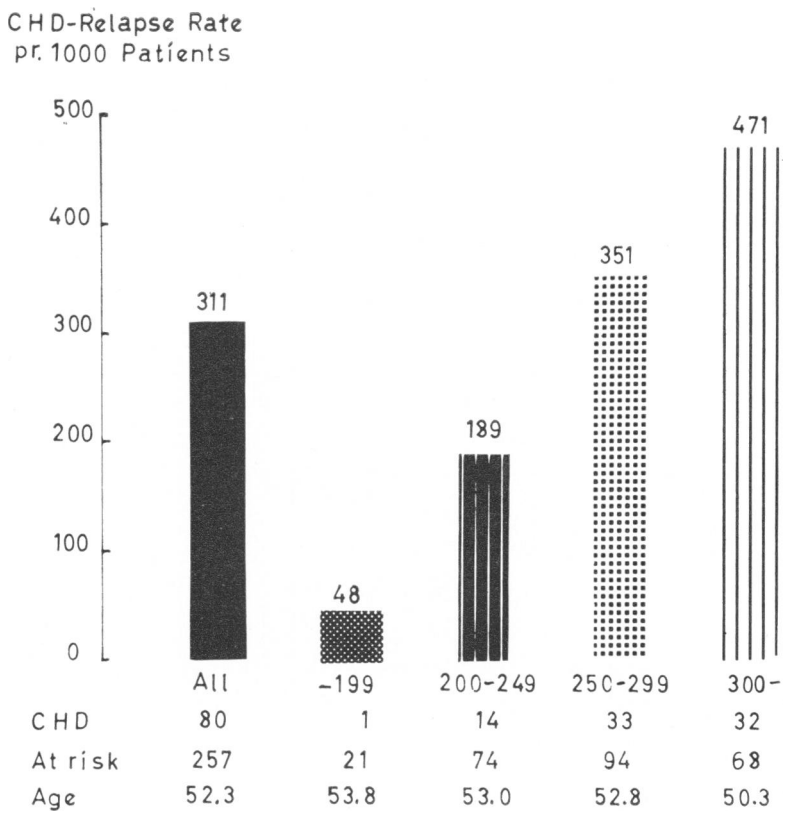

Fig. 4. Both groups together. Age < 60. Incidence of CHD relapses in relation to mean serum-cholesterol level during the period of observation.

was a suggestion, although statistically nonsignificant, toward a higher CHD relapse rate ($x^2 = 2.78$, $p = 0.096$).

The presence of angina pectoris at the start of the trial increased the CHD relapse rate in both groups, especially the incidence of sudden death, which in both groups together was significantly higher in those with angina than in those without ($x^2 = 7.30$, $p = 0.007$). The effect of cholesterol reduction was most pronounced in those who were without angina pectoris at the start of the trial. The difference in the CHD relapse rate between these dieters and controls was highly significant ($x^2 = 10.00$, $p = 0.002$). In those with angina pectoris at the start of the trial the difference in CHD relapse rate between dieters and controls was not statistically significant.

Significantly reduced relapse rate in the dieters as compared with

the controls was found only in those with a normal relative heart volume at the time of the primary infarction.

The presence of a pathological electrocardiogram at the start was accompanied by an increased CHD relapse rate in both groups. This was true especially of the incidence of sudden death, which in both groups together was significantly higher when the ECG was pathological ($x^2 = 11.80$, $p = 0.001$). However, the reduction of the CHD relapse rate in the dieters was the same, whether the ECG at the start of the trial was normal or not.

Investigation of the relation of the CHD relapse rate to the coronary risk factors which can be influenced by preventive measures, namely, serum cholesterol, blood pressure, and tobacco smoking revealed that the serum cholesterol level was the factor which had by far the strongest influence on the CHD relapse rate.

When the groups were analyzed together for this purpose, it appeared that in the normotensives with a low serum cholesterol level, and in the nonsmokers with a low cholesterol level, the CHD relapse rate was significantly reduced as compared to the hypertensives with a high cholesterol and to the smokers with a high cholesterol. The respective tests of significance are: $x^2 = 8.05$, $p = 0.005$ and $x^2 = 9.99$, and $p = 0.002$.

The correlation between the serum cholesterol level and the CHD relapse rate at age below 60 (both groups together) was striking (Figure 4).

In the patients who had overcome their previous myocardial infarction with no obvious signs and symptoms of heart disease, that is, without angina pectoris and with a normal heart volume and a normal blood pressure, a highly significant difference between the diet group and the control group in the total CHD relapse rate was found ($x^2 = 10.15$, $p = 0.001$) (Figure 5).

Discussion

The reduction of the serum cholesterol level in the diet group associated with a reduced CHD relapse rate strongly suggests a cause and effect relation. This contention receives additional support from the finding of a definitely lower serum-cholesterol level in the CHD relapse-free than in those who developed relapses. This distinction applies only to cases with reinfarction—fatal and nonfatal—and to new

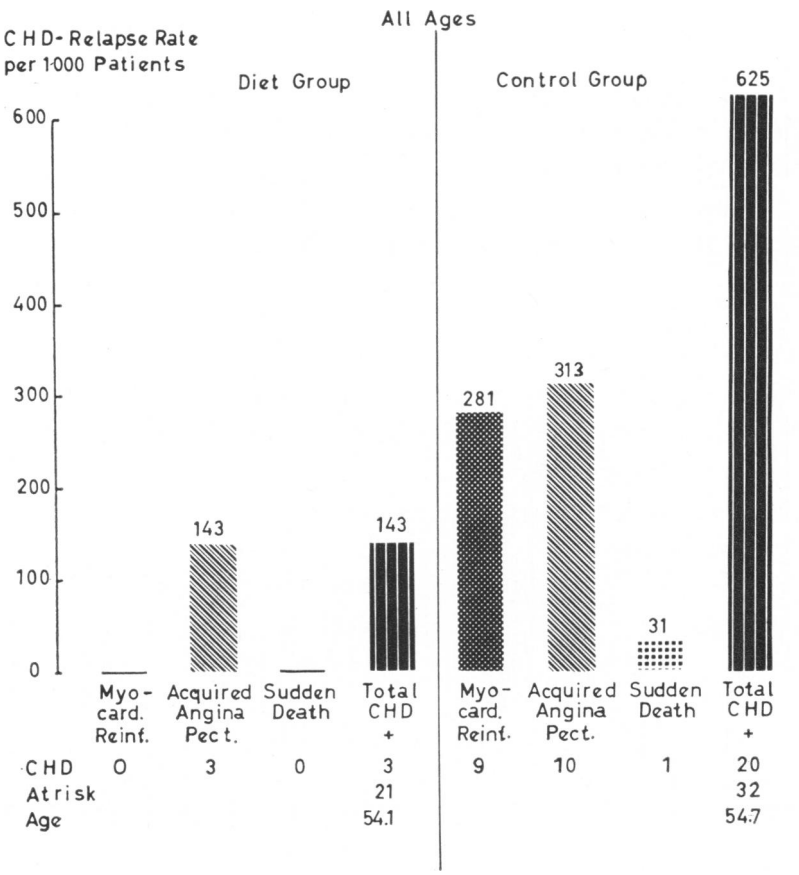

Fig. 5. CHD relapse rate in patients with normal diastolic blood pressure and normal relative heart volume, and without angina pectoris at the start of the trial.

cases of angina pectoris below the age of 60. Significant difference in the CHD relapses between the diet and the control group was also limited to those below 60 years of age.

The preventive value of reduction of plasma cholesterol is further indicated by the finding that the difference between the groups in the incidence of CHD relapses was more pronounced when the serum cholesterol level at the start of the trial was highly elevated.

The incidence of sudden death was not influenced by the diet, nor did the serum cholesterol level of those who died suddenly differ significantly from that of the relapse-free. This observation was not surprising. Although associated with coronary atherosclerosis, sudden death

in survivors of myocardial infarction may not be directly related to the degree of atherosclerosis, but perhaps more to localization. Sudden death is most frequently caused by ventricular fibrillation or cardiac standstill, probably released by ischemia in vital parts such as the conducting system. The absence of influence of the plasma cholesterol level on sudden death in the present study is therefore not irreconcilable with the contention that the prescribed diet was antiatherogenic.

Summary

The effect of a plasma-cholesterol-lowering diet on the CHD relapse rate was studied for five years in a group of 206 male infarction patients. The results were compared with those in another group of 206 patients who continued on a conventional diet. The patients were allocated to the groups after a strictly randomized system, and the groups matched well.

The cholesterol-lowering diet reduced the incidence of total CHD relapses.

There was a distinct difference in the effect on the patients below the age of 60 and those of 60 and over. The difference was highly significant in the younger group but not in the older.

The most striking effect of dietary reduction of the plasma cholesterol was encountered in those who had recovered from their previous myocardial infarction with no obvious signs and symptoms of heart disease. These findings are thought to be applicable to the general population.